Pharmacy Update
November/December 1998

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor-in-Chief
Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information Service, and Clinical Specialist, Endocrinology & Women's Health
kcalis@nih.gov

Associate Editor
Maryam R. Mohassel, Pharm.D.
Specialized Resident in Drug Information Practice and Pharmacotherapy
mmohassel@nih.gov

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Pharmacotherapy of Hyperprolactinemia

Prolactin concentrations greater than 20 µg/L, observed on multiple occasions, are generally considered indicative of hyperprolactinemia. Hyperprolactinemia usually affects women of reproductive age and has been noted in 25% of women with secondary amenorrhea. The incidence of hyperprolactinemia in the general population is reported to be less than 1%.

Hyperprolactinemia has several etiologies. The most common causes are benign prolactin-secreting pituitary tumors, known as prolactinomas, and various medications (Table 1). Prolactinomas are classified according to size. Prolactin-secreting microadenomas are less than 10 mm in diameter and often do not increase in size. In contrast, macroadenomas are tumors with a diameter greater than 10 mm that continue to grow in size and can cause invasion of surrounding tissues. In the presence of a prolactinoma, prolactin serum concentrations may remain normal or may be markedly elevated to thousands of micrograms per liter.

Elevated prolactin serum concentrations inhibit gonadotropin secretion and sex steroid synthesis. Because prolactin concentrations higher than 60 µg/L are associated with anovulation, women with hyperprolactinemia typically present with menstrual irregularities such as oligomenorrhea or amenorrhea and infertility. In addition, approximately 40% to 70% of women with hyperprolactinemia will have galactorrhea. Hyperprolactinemia in men, although rare, may cause decreased libido, erectile dysfunction, infertility, galactorrhea, or gynecomastia. In the presence of a prolactin-secreting pituitary tumor, many patients with hyperprolactinemia may first present with headaches and visual field disturbances that result from tumor compression of the optic chiasm. The prolonged suppression of estrogen in premenopausal women with hyperprolactinemia leads to a decrease in bone mineral density and significant risk for the development of osteoporosis. In addition, untreated hyperprolactinemia in women may increase the risk of ischemic heart disease.

Diagnosis

The diagnosis of hyperprolactinemia, as defined by multiple prolactin serum concentrations above 20 µg/L, is relatively simple. However, identifying the underlying cause of this abnormality may be more challenging. Patients with modest prolactin elevations should have multiple prolactin serum determinations in order to minimize the potential for detecting only transient increases in prolactin. A careful medication history is essential, and the presence of hypothyroidism, renal failure, or hepatic dysfunction should be evaluated. If the cause of hyperprolactinemia remains ambiguous, a computed tomography (CT) scan or magnetic resonance imaging (MRI) study should be performed to determine the presence of a pituitary tumor. If an underlying cause of elevated prolactin serum concentration is not determined, the hyperprolactinemia is considered to be idiopathic.

Treatment

The treatment of hyperprolactinemia depends on the underlying cause of the abnormality. In cases of drug-induced hyperprolactinemia, discontinuation of the offending medication and initiation of an appropriate therapeutic alternative usually normalizes serum prolactin concentrations. In cases where an appropriate therapeutic alternative does not exist, medical therapy with dopamine agonists is warranted. Sex steroid replacement should also be considered. Treatment options for the management of prolactinomas

include clinical observation, medical therapy with dopamine agonists, radiation therapy, and transsphenoidal surgical removal of the tumor. Because prolactin-secreting microadenomas are very small and typically do not increase in size, treatment of these tumors is primarily directed towards alleviating symptoms. The goal of therapy is to normalize prolactin serum concentrations and reestablish gonadotropin secretion in order to restore fertility and reduce the risk of osteoporosis. In patients with asymptomatic elevations in serum prolactin, observation and close follow-up are appropiate. Treatment goals are more aggressive in patients with prolactin-secreting macroadenomas because these tumors are larger and can cause invasion of local tissues with significant visual defects. Therefore, in addition to normalizing prolactin concentrations, tumor shrinkage and correction of visual defects are primary goals of treatment.

Medical therapy with dopamine agonists has proven to be very effective in normalizing prolactin serum concentrations, restoring menstruation, and reducing tumor size in approximately 70% to 100% of patients within 3-6 months of therapy. Bromocriptine (Parlodel®) has been the mainstay of therapy since the 1970's, and pergolide (Permax®) has been used as an effective alternative in patients who are intolerant of the adverse effects associated with bromocriptine. Cabergoline (Dostinex®) is a new long-acting dopamine agonist that offers the advantage of less frequent dosing and may eventually replace bromocriptine as the agent of choice for the medical management of prolactinomas.

Bromocriptine

Bromocriptine was the first D_2-receptor agonist to be used in the treatment of hyperprolactinemia and has been the mainstay of therapy for over 20 years. Medical therapy with bromocriptine normalizes prolactin serum concentrations, restores gonadotropin production, and shrinks tumor size in approximately 90% of patients with prolactinomas.

For the management of hyperprolactinemia, bromocriptine therapy is typically initiated at 1.25 mg to 2.5 mg once daily at bedtime to minimize adverse effects. The dose can be gradually increased by 1.25 mg increments every week to obtain desirable serum prolactin concentrations. Usual therapeutic doses of bromocriptine range from 2.5 mg to 15 mg per day, although some patients may require doses as high as 40 mg per day. Bromocriptine is usually administered in two or three divided doses, but once-daily dosing has also been shown to be effective.

The most common adverse effects associated with bromocriptine therapy include central nervous system symptoms such as headache, lightheadedness, dizziness, nervousness, and fatigue. Gastrointestinal effects such as nausea, abdominal pain, and diarrhea are also common. Bromocriptine should be administered with food to decrease the incidence of adverse gastrointestinal effects. Although most of these adverse effects diminish with continued treatment, about 12% of patients will not tolerate the adverse effects associated with bromocriptine therapy.

Table 1. Drug-induced Hyperprolactinemia

Dopamine antagonists
phenothiazines
haloperidol
metoclopramide
domperidone

Prolactin Stimulators
methyldopa
reserpine
serotonin reuptake inhibitors (SSRIs)
dexfenfluramine
estrogens
progestins
gonadotropin-releasing hormone analogues
benzodiazepines
tricyclic antidepressants (clomipramine and nortriptyline)
monoamine oxidase inhibitors
H_2-receptor antagonists (cimetidine)
Opioids

Other
verapamil

New extended-release dosage forms of bromocriptine are currently being investigated to improve tolerability and compliance. These include a long-acting injectable form of bromocriptine (Parlodel LAR®), which can be administered as monthly intramuscular injections in doses of 50 mg to 75 mg monthly, and a slow-release oral formulation (Parlodel SRO®) that is given as a single daily dose of 5 mg to 15 mg. These formulations have been shown to be as effective as immediate-release bromocriptine and may improve compliance. Vaginal preparations of bromocriptine have also been studied in an effort to decrease the incidence of adverse effects associated with oral dosage forms.

Because most patients with hyperprolactinemia are women with a principal complaint of infertility, the safety of bromocriptine in pregnancy must be considered. One report of over 2,000 pregnancies in women who received bromocriptine during part or all of their gestation did not detect an increase in the risk for spontaneous abortion or incidence of congenital abnormalites. Although bromocriptine does not appear to be teratogenic, some clinicians discontinue therapy as soon as pregnancy is detected because the effects of *in utero* exposure to bromocriptine on gonadal function and fertility of the offspring remains to be determined. In some patients with macroprolactinomas undergoing rapid tumor expansion, bromocriptine therapy must be continued throughout pregnancy.

Pergolide

Pergolide (Permax®) is a dopamine receptor agonist with affinity for both D_1 and D_2 receptors. In the U.S., pergolide is not FDA approved for the treatment of hyperprolactinemia and is most commonly prescribed for the treatment of parkinsonism. However, pergolide has

been used for many years as a safe and effective alternative to bromocriptine in the management of patients with hyperprolactinemia and offers the advantage of one-daily dosing.

For the treatment of hyperprolactinemia, pergolide therapy is initiated at a dose of 25 µg given once daily at bedtime. The average dose that achieves optimal suppression of prolactin serum concentrations is 50 µg per day given as a single dose. Adverse effects of pergolide are similar to those of bromocriptine and include nausea, headache, vomiting, and dizziness in about 30% of patients. The use of pergolide during pregnancy has not been evaluated as extensively as with bromocriptine and should be avoided until additional data become available.

Cabergoline

Cabergoline (Dostinex®) is a new long-acting dopamine agonist with high selectivity and affinity for dopamine D_2 receptors. This agent was approved by the U.S. FDA in 1996 for the treatment of hyperprolactinemia and has been shown to effectively reduce serum prolactin concentrations in 80 - 90% of hyperprolactinemic patients. Cabergoline also effectively reduces tumor size in patients with both micro- and macroprolactinomas. In a multicenter randomized trial comparing the efficacy of cabergoline and bromocriptine, serum prolactin levels were normalized in 83% of patients receiving cabergoline and 58% of patients receiving bromocriptine after 6 months of therapy. Cabergoline may also be effective in patients who are intolerant of or resistant to bromocriptine.

Cabergoline is commercially available as 0.5 mg oral tablets. The initial dose of cabergoline for the treatment of hyperprolactinemia is 0.5 mg once weekly or in divided doses twice weekly. This dose may be increased by increments of 0.5 mg at 4-week intervals based on serum prolactin concentrations. The usual dose is 1 mg - 2 mg weekly; however, doses as high as 4.5 mg weekly have been used. Recent studies have also evaluated the efficacy of a vaginal dosage form of cabergoline to reduce the adverse effects associated with oral therapy.

The most common adverse effects reported with the use of cabergoline are nausea, vomiting, headache, and dizziness. These are similar to the adverse effects reported with bromocriptine and pergolide. However, in a large comparative study evaluating bromocriptine and cabergoline, fewer patients receiving cabergoline reported adverse effects than patients receiving bromocriptine, and only 3% of the patients in the cabergoline group withdrew from the study due to adverse effects versus 12% of patients taking bromocriptine. Other adverse events associated with the use of cabergoline include gastrointestinal complaints, drowsiness, fatigue, paresthesias, dyspnea, suffocation sensation, and epistaxis. As with other dopamine agonists, adverse events usually occur early in therapy and subside with continued treatment. However, in one study 15% - 20% of patients receiving cabergoline experienced a recurrence of early symptoms or an onset of new symptoms after several weeks of treatment. Mild to moderate decreases in blood pressure have been observed in up to 50% of patients taking cabergoline; however, the incidence of symptomatic orthostatic hypotension has not been significant. Several patients have experienced clinically insignificant decreases in hemoglobin. This was attributed to the restoration of menses in previously amenorrheic patients. Transient increases in serum alkaline phosphatase, bilirubin, and aminotransferases have been reported in small numbers of patients receiving cabergoline. Pleuropulmonary disease has been reported with cabergoline, but only with larger doses used in the treatment of Parkinson's disease.

The use of cabergoline in pregnancy has not been extensively studied. However, several case reports of women who received cabergoline therapy during the first and second trimesters of pregnancy have not documented an increased risk of spontaneous abortion, congenital abnormalities, or tubal pregnancy. However, prospective data in large numbers of pregnancies is lacking. Due to the long half-life and limited data on cabergoline use in pregnancy, most clinicians recommend that women receiving cabergoline therapy who plan to become pregnant should discontinue the medication one month before planned conception.

Monitoring

Prolactin serum concentrations should be monitored every 3 to 4 weeks after the initiation of any dopamine agonist therapy to assess efficacy and appropriately titrate medication dosage. In addition, symptoms such as headache, visual disturbances, menstrual cycles in women, and sexual function in men should be evaluated to assess clinical response to therapy. Once prolactin concentrations have normalized and clinical symptoms of hyperprolactinemia have resolved with dopamine agonist therapy, prolactin serum concentrations should be monitored every 6-12 months. In patients receiving long-term treatment, the medication can be discontinued every 5 years to determine if remission has occurred.

Conclusions

Hyperprolactinemia is a common disorder that can have a significant impact on fertility. Hyperprolactinemia is most commonly due to the presence of prolactin-secreting pituitary tumors and various medications that antagonize dopamine or increase the secretion of prolactin. Available treatment options for this disorder include medical therapy with dopamine agonists, radiation therapy, and transsphenoidal surgery. In most cases, medical therapy with dopamine agonists is considered the most effective treatment, and bromocriptine has been the mainstay of therapy. Cabergoline, a new dopamine agonist, appears to be better tolerated than bromocriptine and is at least as effective if not more effective than bromocriptine. Although additional studies are needed to confirm its benefits, cabergoline may soon replace bromocriptine as the mainstay of medical therapy.

References available upon request.

Did You Know . . .

- The FDA recently approved leflunomide (Arava®, Hoechst-Marion Roussel), an isoxazole derivative with antiinflammatory and immunosuppressant activity, for the treatment of active rheumatoid arthritis. Leflunomide should not be administered to pregnant women or women of child bearing age who are not using reliable contraception.
- Rotashiled (rotavirus vaccine, live, oral, tetravalent), manufactured by Wyeth-Ayerst, is the first vaccine approved for the prevention of rotavirus infections. These infections can lead to nausea and diarrhea in approximately 80% of infected children over five years of age.
- Thalidomide (Thalomid®, Celgene) was approved for the treatment of skin lesions due to leprosy. To ensure that thalidomide is used safely, access to this medication is restricted to physicians and patients who are registered with the manufacturer. Since thalidomide can lead to severe birth defects, women of child bearing age must have repeated pregnancy tests and use two forms of contraception while on this medication.
- Sevelamer (Renagel®, GelTex Pharmaceuticals), a polymeric phosphate binder, was approved by the FDA for the reduction of serum phosphorous concentrations in patients with end-stage renal disease. This agent is free of aluminum and calcium, and exerts its action by binding to dietary phosphorus.
- Fomivirsen (Vitravene®, Isis Pharmaceuticals and Ciba Vision), an antisense agent, was recently approved for the treatment of cytomegalovirus retinitis in patients with AIDS. It is administered as an intravitreal injection and is used in patients who are intolerant of or have failed other treatments for CMV retinitis.

Formulary Update:

The Pharmacy and Therapeutics Committee recently approved the following formulary actions:

Additions:

- Alpha interferon / ribavirin (Rebetron®), for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha interferon therapy alone
- Meropenem (Merrem®), a broad-spectrum carbapenem antibiotic
- Efavirnez (Sustiva®), a non-nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV-1 infected adults and children
- Ofloxacin ophthalmic solution (Ocuflox®), a topical flouroquinilone antibiotic
- Lodoxamide ophthalmic solution (Alomide®), a mast cell stabilizer used for the treatment of keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
- Brimonidine ophthalmic solution (Alphagan®), an alpha-2 adrenergic agonist used for the treatment of open-angle glaucoma and ocular hypertension
- Carboxymethylcellulose ophthalmic solution (Refresh Plus®), an eye lubricant

Deletions:

- Elase® Ointment

Editors' Note

We wish to thank Amy M. Heck, Pharm.D. and Jack A. Yanovski, M.D., Ph.D. for their contribution to this issue of *Pharmacy Update.*

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301-496-2407

Pager #104-2619-7 or 104-5264
Building 10, Room 1S-259

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196